# Common polymorphisms in genes related to vitamin D metabolism affect the response of cognitive abilities to vitamin D supplementation

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# Common polymorphisms in genes related to vitamin D metabolism affect the response of cognitive abilities to vitamin D supplementation

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**Running title:** Vitamin D and cognition

**Abstract**

It is possible that vitamin D acts as a neurosteroid, and that vitamin D deficiency may have an adverse impact on brain function and cognitive function. There are a few reports that have demonstrated an association between polymorphisms of genes involved in vitamin D metabolism, and neurodegenerative disease. We aimed to evaluate the relationship between common, functional vitamin D-associated gene variants and cognitive abilities, and to investigate the effect size of this polymorphism on cognitive capabilities associated with high dose vitamin D supplementation. A total of 319 healthy adolescents received a high dose of vitamin D (50,000 IU)/week for 9 weeks. A questionnaire was used to assess cognitive abilities at baseline and after treatment. The genotypes of the CYP2R1-rs10766197 and GC-rs4588 variants were determined using TaqMan genotyping techniques. At baseline total cognitive ability scores were higher in the AA group who were homozygous for the uncommon allele, compared to the other (AG and GG) genotypes of the *CYP2R1*-rs10766197 polymorphism (104.9±27.8 vs. 79.1±38.8 vs. 73.1±25.6; $p < 0.001$, respectively). During the supplementation period, cognitive ability scores increased in individuals with the AG and GG genotypes, whilst individuals with a AA genotype did not show significant change in total score after intervention ($p=0.17$). For GC SNP (rs4588), no major differences at baseline and trial-net change of cognitive tasks score were observed between genotypes under three genetic models ($p_{SNP}=0.67$). Vitamin-D supplements have trait-dependent effects on cognitive performance that suggests a causal role for vitamin D in cognitive performance. The rs10766197 variant, near the CYP2R1 gene locus, significantly modified the efficacy of high dose vitamin D3 supplementation for its effects on improving cognitive abilities indicate that some subjects might require a higher dose to benefit from in terms of cognitive performance.

**Keywords:** memory, planning, variation, cytochrome P450 family, group specific component

## 1. Introduction

There is growing evidence that an inadequate dietary intake of essential micronutrients such as vitamins and minerals may have an adverse impact on brain function and cognitive ability (Prado and Dewey, 2014, McCann et al., 2006).

Vitamin D is a fat-soluble vitamin, with some of the properties of a steroid hormone. It is primarily produced in the skin from 7 dehydrocholesterol (previtamin D) through solar UV-B exposure and also obtained to a lesser degree from dietary intake. Both circulating serum levels and polymorphisms in genes related to vitamin D metabolism are correlated with several conditions/disorders such as metabolic and inflammatory diseases, common cancers, as well as dementias and cognitive impairments (Holick and Chen, 2008, Shah et al., 2012, Grant et al., 2017).

The molecular basis underlying the roles of vitamin D on human brain development are diverse. The ubiquitous distribution of vitamin D receptor (VDR) and two enzymes involved in terminal activation of calciteriol (25-hydroxylase and1,α-hydroxylase) throughout the brain as well as presence of vitamin D target genes in central nervous system (CNS) which induced neurogenesis highlighted the importance of vitamin D for normal cognitive function(McCann and Ames, 2008).

Multiple calcium-binding proteins are found in the brain (Zhang et al., 2014) and vitamin D-enhanced calcium homeostasis can also protect against cognitive decline. It has been shown that one vitamin D-related protein, calbindin-D, which modulate intra-cellular calcium amounts in neurons was significantly decreased in the hippocampus tissue from Alzheimer's disease (AD) (Sutherland et al., 1992). In vitro experiments have supported potential anti-inflammatory, neurotrophic and neuroprotective potential of calciteriols (Ślusarczyk et al., 2016, Kajta et al.,

2009), as vitamin D supplementation could delay hippocampal ageing in experimental animal studies (Brewer et al., 2006). In VDR knockout mice, vitamin D deficiency may be possibly linked with ageing, hearing loss, communicative, motor and sensory deficits (Keisala et al., 2009, Zou et al., 2008).

Neuroepidemiologic studies have reported associations between hypovitaminosis D and age-related cognitive difficulties, impaired neurocognitive performance, dementia and schizophrenia risk (Breitling et al., 2012, Feart et al., 2017, Miller et al., 2015, Noublanche and Annweiler, 2016, Itzhaky et al., 2012). Although, other studies have not supported this association (Norelli et al., 2010, Tolppanen et al., 2011, Slinin et al., 2010, McGrath et al., 2007). Indeed, results from interventional studies that have assessed the effects of vitamin D supplementation on cognitive performance have not been positive (Rossom et al., 2012, Dean et al., 2011, Stein et al., 2011). Taken together, the association between vitamin D and cognitive function is not yet completely established.

SNPs in the vitamin D binding protein or group specific component (*DBP/GC*), which transports vitamin D metabolites, and the Cytochrome P450, family 2, subfamily R, polypeptide 1 (*CYP2R1*) as a 25-hydroxylase, which catalyzes the transformation of vitamin D3 to its main circulating metabolite 25(OH)D3, have previously been shown to affect serum vitamin D levels in different populations. Moreover, healthy individuals with various CYP2R1 or DBP genotypes have different magnitude responses to the similar vitamin D dose (Fu et al., 2009, Bahrami et al., 2018b). Genetic variability may therefore explain differences in vulnerability to cognitive dysfunction and incidence of cognitive impairments. There are few studies that have demonstrated associations between polymorphism of vitamin D-associated genes (i.e. VDR, megalin, GC, CYP27B1 and CYP2R1) and neurodegenerative condition (Keyimu et al., 2014,

Alfred et al., 2013, Beydoun et al., 2012, Lehmann et al., 2011), and none so far have examined the effects of vitamin D supplements on cognitive function.

Taking into account these conflicting findings, we aimed to evaluate the relationship between the common, functional vitamin D-associated gene variants and cognitive abilities, and to investigate the effect of this polymorphism on cognitive capabilities scores in response to vitamin D supplementation.

## 2. Material and Method:

### *2.1. Study design*

Three hundred and nineteen adolescent girls aged between 12-18 years were recruited between January and April 2015 in Mashhad City, using a randomized cluster sampling method. Informed consent was signed by all participants and their parents and study protocols approved by the Ethics Committee of the Mashhad University of Medical Sciences (MUMS). Participants with any history of chronic diseases, metabolic disorders, cancer or who were taking any types of anti-depressant or psychotropic agents were excluded from study. Participants received high dose vitamin D (capsule containing 50,000 IU vitamin D per week) for 9 weeks.

### *2.2. Cognitive abilities assessment*

A Cognitive abilities questionnaire (CAQ) was used to assess a number of cognitive functions, that included: memory, inhibitory control, selective and sustained attention, decision making, planning, social and flexibility of cogitation(NEJATI, 2013). CAQ encompasses 30 independent items which are rated on a 5-point Likert scale (1-5) and provided a total score of 30-150. Higher scores indicate superior cognitive function. This questionnaire fulfill by study subjects at baseline and after 9 weeks of supplementation.

### *2.3. Genotyping*

Two candidate gene loci were investigated in the present study: the CYP2R1 (rs10766197) and GC (rs4588), that have been shown to be involved in the synthesize and transport vitamin D as well related with neurological diseases in previous studies (Bahrami et al., 2018c). Blood specimens were collected from all of the participants after overnight fasting. DNA was isolated from the peripheral blood using QIAamp-DNAMini-Kit (Qiagen, San Diego, CA) in accordance with the manufacturer's instructions. The DNA concentration and purity were measured using NanoDrop-1000-Detector (Nano-Drop-Technologies, Wilmington, USA). Genotyping was performed using a TaqMan allelic discrimination assay with ~20 ng of DNA in the total 12.5 ml volume PCR reaction (Applied Biosystems Foster City, CA). Allelic content of each sample was determined by ABIPRISM-7500 machine with the SDS analysis software.

*2.4. Statistics analysis*

Data were analyzed using SPSS version 16 (SPSS Inc., IL, USA) and GraphPad Prism version 3 softwares. Variables are reported as mean ± standard deviation (SD). The normality of variables was examined by Kolmogorov–Smirnov test. Independent sample T-test or ANOVA was used to compare changes in task scores after supplementation in different genotype groups. Chi-square tests checked agreement of genotypic frequencies to those of Hardy-Weinberg equilibrium. ANCOVA test was conducted to investigate the effect of the genotypes on cognition score in response to supplementation. Logistic regression analysis clarifies the probability of change in cognition scores across various genetic models. A P value less than 0.05 considered statistically significant.

## 3. Results

Baseline characteristics of participants included in this interventional study, as well as effect of high dose vitamin D supplementation on different biochemical and metabolic parameters have been reported previously(Bahrami et al., 2018a). As we have shown serum vitamin D concentrations were significantly increased after the vitamin D supplements (9.4±8.8 ng/ml *vs.* 36.4±15.4 ng/ml, $p<0.001$)(Bahrami et al., 2018a). Allele frequencies of variation were in Hardy-Weinberg equilibrium ($p=0.35$).

To evaluate the association between the CYP2R1 (rs rs10766197) and GC (rs4588) variants on cognitive ability tasks score after supplementation, participants were grouped based on their genotype (Table 1).

**Cytochrome P450 Gene variant**-Regarding to *CYP2R1*-rs10766197, at baseline total cognitive abilities score was higher in AA group (homozygous for uncommon allele) compared to AG and GG genotypes (104.9±27.8 vs. 79.1±38.8 vs. 73.1±25.6; $p<0.001$, respectively). During the supplementation period, cognitive ability scores increased in the girls with a AG or GG genotype, although AA genotype did not show a significant change in their total score after the intervention ($p=0.17$). The rs10766197 SNP of the *CYP2R1* gene appeared to modulated cognitive tasks scores in response to intervention ($p_{\text{intervention}} <0.001$ and $p_{\text{SNP}}= 0.05$) (Figure1.A). Further sub-analysis showed that memory, inhibitory control and selective attention, decision making, planning, and sustain attention scores increased after 9 week supplementation in all participants but subjects with GG genotype revealed a greater increment (Table 1). Interestingly, social cognition was reduced in the AG and GG carriers, whilst the subjects with AA genotypes, there was a small increase after vitamin D supplements, but this change was not statistically significant using three genetic models (dominant, additive and recessive models). Also, cognitive flexibility only increased in GG and AG genotype groups (Table 1).

Regression analysis also showed that the probability of change in the scores of tasks including memory, inhibitory control and selective attention, decision making, planning and total cognitive abilities after intervention, in persons who had homozygous major allele GG was higher those had the homozygous for uncommon A allele after adjustment for confounding variables that included: age, BMI percentile and serum vitamin D at baseline ($p<0.05$). The regression analysis also showed a significant effect using both dominant and recessive models after adjustment for potential confounders ($p <0.05$) (Table 2).

**GC/DBP variant**-For GC SNP (rs4588), no major differences at baseline and trial-net change of cognitive tasks score were observed between genotypes under three genetic models($p_{SNP}=0.67$) (Figure1.C). Hence, these changes were not attributable to the GC polymorphisms, since during follow-up no differences in measures of cognitive abilities were seen for carriers of this polymorphism (Table 1).

**4. Discussion**

To the best of our knowledge this is the first study to explore the relationship between variations at vitamin D-associated genes with cognitive ability and demonstrated that *CYP2R1*-rs10766197 variation was significantly related with the baseline score and change in cognitive abilities score after nine weeks of vitamin D administration. Our analyses indicate that, on average, subjects with a dominant G allele responded favorably to vitamin D, with enhanced cognitive abilities score.

Another SNP (in *GC*) was not associated with baseline cognitive abilities score and did not show a significant impact on the response to supplementation. The reason for this is unknown. It may be due to the small sample size and thereupon limited power.

The multiple positive but weak associations are a frequent finding in complex diseases. For vitamin D status, more than 20 genes have now been reported to be modifiers but no single gene has been found to rigorously involve in risk in all populations evaluated (Bahrami et al., 2018c). Clearly there are small genetic effects with large heterogeneity; occasionally there is unrecognized population stratification and there plausible occur phenotyping and genotyping mistakes.

We investigated variants that have been consistently related with circulating vitamin D levels (Bahrami et al., 2018c). CYP2R1 is a member of the CYP2 family that encodes cytochrome P450 proteins. This enzyme specifically hydroxylates cholecaliferol at the 25-C position to generate 25-hydroxyvitamin D in the liver (Bahrami et al., 2018c). The SNP-rs10766197 is located in the promoter region of the *CYP2R1* gene. GC as a member of the albumin family codifies DBP which is the principal transporter for vitamin D metabolites in the circulation. SNP-rs4588 is in exon 11 of GC and maybe cause defects in function of GC (Bahrami et al., 2018c). Data from 1207 subjects in the Baltimore Longitudinal Study of Aging with mean 10.4 years follow-up showed that vitamin-D influences brain performance trait-dependently during aging. *GC* gene polymorphisms are associated with poorer performance in executive function, visuospatial, and verbal abilities. Although there did not observe any relationships between GC composite SNP score and memory performance (Kueider et al., 2016). Similarly, in a case-control study performed by Schmidt *et al.* child *CYP2R1* (rs10741657) and *GC* (rs4588) variants showed no association with risk of autism spectrum disorder in the logistic regression model(Schmidt et al., 2015). Pooled analysis of 16,527 individuals aged >44 years from the UK demonstrated among different items of cognitive capability including word recall, semantic

fluency, phonemic fluency, and search speed , the T allele of rs2282679 (GC) was only related with fewer word recall scores (β = 20.0, 95% CI: 20.05, 20.003; P = 0.03)(Alfred et al., 2013).

The effects of genetic variation in vitamin-D related SNPs on specific cognitive abilities become to be more comprehensive than the effects of serum/plasma vitamin-D levels alone. Notably, we observed an association between the rs-107661697 polymorphism on cognitive function at baseline, suggesting that genetic predisposition is associated with lower cognitive abilities, these individuals show enhanced increments in cognition during trial.

Interpretation of relationship between vitamin D and cognitive function is complicated. In a Mendelian randomization study, Maddock *et al,* found no associations between *DHCR7* and *CYP2R1*SNPs*/synthesis score* with global and memory cognition even after stratifying by gender, age and vitamin D tertiles (Maddock et al., 2017). In other Mendelian randomization analysis, SNPs contributed in metabolism of vitamin D including GC (rs2282679) and CYP24A1 (rs6013897) to be potent predictors of AD risk by increasing the 46% odds of AD (CI: 1.03–2.07; p= 0.032). In contrast, a null effect we found for SNPs contributed in the synthesis of vitamin D including DHCR7 (rs12785878) and CYP2R1 (rs10741657) on AD ($OR_{synthesis}$ =1.17, 95%CI: 0.9–1.5) (Mokry et al., 2016).

Gezen and colleagues examined whether there is link between the *VDR* gene and late-onset AD. Regarding to ApaI genotypes, the frequency of the AA genotype was considerably significantly higher in AD patients compared to healthy individuals ($p$ = 0.008, $\chi^2$ = 9.577, OR = 2.30), but the TaqI genotype distribution was not different between the two groups. Thus, this study supported the potential association between AD and vitamin D. Indeed, “AT” haplotype was more common in controls, suggesting a protective role for AD(Gezen-Ak et al., 2007).

Adolescence is associated with an elevated need to regulate impact and behavior. Since maturation and the developing brain during adolescence, mental, behavioral and cognitive networks occur with different speed; this time is usually one of the higher vulnerability and modification. Therefore, normative progression in adolescence can beneficially be followed with respect to the coordination of emotional, intelligence, subconscious and behavioral tendencies and abilities, and psychopathology in adolescence may be representative of challenging in this coordination trend (Steinberg, 2005).

The current study has several strengths: First, by performing this study on healthy subjects, the analysis of the genetic effect on cognitive abilities score is not confounded by the plausible effect of other diseases; second, selected rigorous genetic marker this previously demonstrated in GWASs implied in vitamin D metabolism; and third, all of trial were taken during the winter to make effect of sun exposure least. The main limitation of the study was the lack of a placebo group due to the ethical considerations.

**5. Conclusion**

Taken together, we observed that vitamin-D has trait-dependent effects on cognitive performance which provides evidence to support a causal role for vitamin D in cognitive performance. In novel analyses, we found one SNP that significantly modified the efficacy of mega dose vitamin D3 supplementation for improving cognitive abilities: rs10766197 near *CYP2R1*, indicating that some subjects might require a higher dose to benefit from better cognitive performance. Since we did not find any previous investigations on the association between genetic polymorphisms of genes-related vitamin D and cognitive abilities in response to supplementation, this result may need confirmation to elucidate the physiological context for the genetic associations.

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